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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,197	08/20/2003	William M. Pardridge	306J-002100US	3519

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EXAMINER	
LANDAU, SHARMILA GOLLAMUDI	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
11/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/647,197	PARDRIDGE ET AL.	
	Examiner	Art Unit	
	Sharmila Gollamudi Landau	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *1-8 and 43-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 9-42 in the reply filed on 8/15/07 is acknowledged. Claims 1-8 and 43-50 are withdrawn as being directed to a non-elected invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 9-42 are rejected under 35 U.S.C. 102(a) as being anticipated by Olivier et al (Synthesis of Pegylated Immunoparticles, Pharmaceutical Research, Vol. 19, No. 8, August 2002).

Olivier et al disclose pegylated nanoparticles comprising PLA-PEG_{3500}-maleimide and methoxyPEG_{2600}-PLA in a ratio of 1:30. See abstract and page 1141. The s core of the particle comprises a drug and PEG strands form a corona, which are conjugated to a antibody via melamine. See Figure 1. The nanoparticles have a size of 100nm. See page 1140.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 9-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pardridge (6,372,250) in view of Gref et al (5,565,215).

Pardridge teaches non-invasive gene targeting to the brain. Pardridge teaches neutral liposome having an exterior surface and an internal compartment in which the therapeutic gene is located. The surface of the liposome is decorated with several thousand strands of polyethyleneglycol (PEG). The PEG strands prevents the rapid absorption of blood proteins to the surface of the liposome, which is what accelerates the rapid removal from blood of unprotected liposomes. The molecular weight of PEG is preferably between 1000 and 50,000 DA. A particularly preferred conjugation agent is a bifunctional 2000 DA PEG which contains a lipid at one end and a maleimide group at the other end. The lipid end of the PEG binds to the surface of the liposome with the maleimide group bonding to the receptor-specific monoclonal antibody or other blood-brain barrier targeting vehicle. See column 5, lines 50-65. The pegylated liposomes are protected and are removed from blood at a much slower rate. Further, the liposomes under receptor-mediated endocytosis into target cells in brain because the surface of the liposome is decorated with "transportable peptides". See column 2, lines 30-60. The transportable peptide is a peptide that is conjugated to a maleimide group on the tip of the PEG

strand. See column 6, lines 1-15. Pardridge teaches attaching 5 to 1000 targeting vehicles be conjugated to each liposome. See column 5, lines 50-65. The pegylated liposomes are a mixture of 0.6 micromol DSPE-PEG_{2000}-maleimide and 30nmol DSPE-PEG_{2000}. See column 7, lines 45-65 and Figure 1.

Pardridge teaches that although the invention is described using liposomes as the preferred nanocontainer, other nanocontainers may be used. For example, the liposome can be replaced with a nanoparticle or any other molecular nanocontainer with a diameter <200 nm that can encapsulate the DNA and protect the nucleic acid from nucleases while the formulation is still in the blood or in transit from the blood to the intracellular compartment of the target cell. See column 6, lines 15-35.

Although the reference suggests the use of other nanocontainers, Pardridge does not specify a polymeric nanosphere.

Gref teaches nanoparticles that are not rapidly cleared from the blood stream by the macrophages of the reticuloendothelial system, and that can be modified to target specific cells or organs as desired. Gref teaches the polymeric particles may be manipulated to control the release rate of the drug. The particles have a biodegradable solid core containing a biologically active material and/*or* contrast agent for imaging and poly(alkylene glycol) moieties on the surface. The terminal hydroxyl group of the poly(alkylene glycol), PEG specifically, can be used to covalently attach onto the surface of the particles biologically active molecules, including antibodies targeted to specific cells or organs, or molecules affecting the charge, lipophilicity or hydrophilicity of the particle. The typical size of the particles is between 1 nm and 1000 nm, preferably between 1 nm and 100 nm, and the ideal size is less than 200nm. See column 2, lines

30-50 and column 4, lines 1-5. Many polymers may utilized to fabricate the nanoparticles including polylactic acid. See column 4, lines 50-67, column 9, lines 35-55, and examples. PEG has a molecular weight of 5000-20,000. see column 11, lines 5-35.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Pardridge and Gref et al and utilizing a polymeric substance such as instantly claimed polymers in place of the liposome forming lipid, i.e. DSPE taught by Pardridge. One would have been motivated to do so with a reasonable expectation of success and similar results since Pardridge suggests the use of other nanocontainers with the critical element being the encapsulation of the active in the core and having a size of less than 200nm. Gref teaches a nanosphere made from polymers that protect the bioactive molecule with a size of less than 200nm and target specific cells. Further, a skilled artisan would have been motivated to specifically utilize polymers over the lipids if one desired to manipulate the release rate of the drug as taught by Gref et al. Therefore, it would have been prima facie obvious to utilize a polymeric substance to form the nanoparticle versus a lipid, which forms a liposome.

Regarding claims 18-19 and 33-34, note the functionalized composition will have a greater molecular weight since the functionalized strands further comprise the conjugation agent, i.e. maleimide, and the targeting agent, i.e. such as an antibody.

Regarding claims 39-40, Pardridge teaches attaching 5 to 1000 targeting vehicles be conjugated to each liposome. Depending on the desired targeting agents attached to the nanparticle, it would have been obvious to manipulate the non-functionalized composition and functionalized composition.

Note that PEG moieties implicitly orient themselves around the core to form a "corona".

Claims 9-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pardridge (6,372,250) in view of Gref et al (5,565,215) in further view of Olivier et al (Synthesis of Pegylated Immunoparticles, Pharmaceutical Research, Vol. 19, No. 8, August 2002).

Pardridge teaches non-invasive gene targeting to the brain. Pardridge teaches neutral liposome having an exterior surface and an internal compartment in which the therapeutic gene is located. The surface of the liposome is decorated with several thousand strands of polyethyleneglycol (PEG). The PEG strands prevents the rapid absorption of blood proteins to the surface of the liposome, which is what accelerates the rapid removal from blood of unprotected liposomes. The molecular weight of PEG is preferably between 1000 and 50,000 DA. A particularly preferred conjugation agent is a bifunctional 2000 DA PEG which contains a lipid at one end and a maleimide group at the other end. The lipid end of the PEG binds to the surface of the liposome with the maleimide group bonding to the receptor-specific monoclonal antibody or other blood-brain barrier targeting vehicle. See column 5, lines 50-65. The pegylated liposomes are protected and are removed from blood at a much slower rate. Further, the liposomes under receptor-mediated endocytosis into target cells in brain because the surface of the liposome is decorated with "transportable peptides". See column 2, lines 30-60. The transportable peptide is a peptide that is conjugated to a maleimide group on the tip of the PEG strand. See column 6, lines 1-15. Pardridge teaches attaching 5 to 1000 targeting vehicles be conjugated to each liposome. See column 5, lines 50-65. The pegylated liposomes are a mixture of 0.6 micromol DSPE-PEG_{2000}-maleimide and 30nmol DSPE-PEG_{2000}. See column 7, lines 45-65 and Figure 1.

Pardridge teaches that although the invention is described using liposomes as the preferred nanocontainer, other nanocontainers may be used. For example, the liposome can be replaced with a nanoparticle or any other molecular nanocontainer with a diameter <200 nm that can encapsulate the DNA and protect the nucleic acid from nucleases while the formulation is still in the blood or in transit from the blood to the intracellular compartment of the target cell. See column 6, lines 15-35.

Although the reference suggests the use of other nanocontainers, Pardridge does not specify a polymeric nanosphere.

Gref teaches nanoparticles that are not rapidly cleared from the blood stream by the macrophages of the reticuloendothelial system, and that can be modified to target specific cells or organs as desired. Gref teaches the polymeric particles may be manipulated to control the release rate of the drug. The particles have a biodegradable solid core containing a biologically active material and/*or* contrast agent for imaging and poly(alkylene glycol) moieties on the surface. The terminal hydroxyl group of the poly(alkylene glycol), PEG specifically, can be used to covalently attach onto the surface of the particles biologically active molecules, including antibodies targeted to specific cells or organs, or molecules affecting the charge, lipophilicity or hydrophilicity of the particle. The typical size of the particles is between 1 nm and 1000 nm, preferably between 1 nm and 100 nm, and the ideal size is less than 200nm. See column 2, lines 30-50 and column 4, lines 1-5. Many polymers may utilized to fabricate the nanoparticles including polylactic acid. See column 4, lines 50-67, column 9, lines 35-55, and examples. PEG has a molecular weight of 5000-20,000. see column 11, lines 5-35.

Olivier et al disclose pegylated nanoparticles comprising PLA-PEG_{3500}-maleimide and methoxyPEG_{2600}-PLA. Olivier et al teach nanoparticles made of polymers have the advantage over liposomes in that they can be freeze-dried for a long term. See page 1137.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Pardridge and Gref et al and utilizing a polymeric substance such as instantly claimed polymers in place of the liposome forming lipid, i.e. DSPE taught by Pardridge. One would have been motivated to do so with a reasonable expectation of success and similar results since Pardridge suggests the use of other nanocontainers with the critical element being the encapsulation of the active in the core and having a size of less than 200nm. Gref teaches a nanosphere made from polymers that protect the bioactive molecule with a size of less than 200nm and target specific cells. Further, a skilled artisan would have been motivated to specifically utilize polymers over the lipids if one desired to manipulate the release rate of the drug as taught by Gref et al. Therefore, it would have been prima facie obvious to utilize a polymeric substance to form the nanoparticle versus a lipid, which forms a liposome.

Further, a skilled artisan would have been motivated to specifically utilize a nanoparticle made of polymers over liposome forming materials to provide long term storage by freeze-drying as taught by Olivier.

Regarding claims 18-19 and 33-34, note the functionalized composition will have a greater molecular weight since the functionalized strands further comprise the conjugation agent, i.e. maleimide, and the targeting agent, i.e. such as an antibody.

Regarding claims 39-40, Pardridge teaches attaching 5 to 1000 targeting vehicles be conjugated to each liposome. Depending on the desired targeting agents attached to the

nanparticle, it would have been obvious to manipulate the non-functionalized composition and functionalized composition.

Note that PEG moieties implicitly orient themselves around the core to form a "corona".

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila Gollamudi Landau whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharmila Gollamudi Landau
Primary Examiner
Art Unit 1616

10/22/07